CLAIMS

1. Process for preparation of crystalline forms of the optical enantiomers of modafinil, comprising the following stages :

i) dissolving one of the optical enantiomers of modafinil in a solvent other than ethanol,

ii) crystallising the enantiomer of modafinil,

iii) recovering the crystalline form of the enantiomer of modafinil so obtained.

2. Process according to claim 1, in which the modafinil enantiomer is the laevorotatory enantiomer .

3. Process according to claim 1, in which the modafinil enantiomer is the dextrorotatory enantiomer.

4. Process according to any one of claims 1 to 3, in which the crystalline form obtained is a polymorphic form.

5. Process according to any one of claims 1 to 4, in which crystallisation is performed under kinetic or thermodynamic conditions.

6. Preparation process according to claim 5, in which crystallisation is performed by precipitation, possibly in the presence of seeds of crystals of the desired crystalline form.

7. Preparation process according to claim 5, in which crystallisation consists of cooling the solution obtained in stage i).

8. Process according to claim 7, in which cooling is slow.

9. Process according to claim 7, in which cooling is fast.

10. Process according to claims 4 and 8, in which the solvent used in stage i) is selected from acetone, 1-4 dioxan, ethyl acetate, ortho, meta or para xylene, or a mixture of ortho, meta and/or para xylene, and the polymorphic form so obtained is then described as Form I.

11. Process according to claims 4 and 9, in which the solvent used in stage i) is selected from methanol, water or alcohol/water mixtures, the crystalline form then obtained being described as Form I.

12. Process according to claims 4 and 9, in which the solvent used in stage i) is isopropanol, n-propanol, ethyl acetate or ethanol denatured with toluene, the polymorphic form so obtained being described as Form II.

13. Process according to claims 4 and 8, in which the solvent used in stage i) is isopropanol, the polymorphic form so obtained being described as Form II.

14. Process according to claims 4 and 9, in which the solvent used in stage i) is acetone, the polymorphic form so obtained being described as Form III.

15. Process according to claims 4 and 8, in which the solvent used in stage i) is selected from tetrahydrofuran, chloroform, methylethylketone, the polymorphic form so obtained being described as Form IV.

16. Process according to any one of claims 1 to 3, in which the crystalline form obtained is a solvate.

17. Process according to claims 8 and 16, in which the solvent used in stage i) is dimethyl carbonate, the solvate so obtained being described as the dimethyl carbonate solvate.

18. Polymorphic form of the laevorotatory or the dextrorotatory enantiomer of modafinil described as Form II, characterised in that it produces an X-ray

diffraction spectrum comprising intensity peaks at the interplanar spacings : 8.54, 7.57, 7.44, 4.56, 3.78, 3.71 (Å).

19. Polymorphic form according to claim 18, characterised in that it produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 11.33, 8.54, 7.57, 7.44, 5.67, 5.33, 4.83, 4.59, 4.56, 4.45, 4.05; 3.88, 3.78, 3.71, 3.34, 2.83, 2.53 (Å).

20. Polymorphic form of the laevorotatory or the dextrorotatory enantiomer of modafinil described as Form III, characterised in that it produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 12.28, 8.54, 5.01, 4.10, 3.97, 3.20 (Å).

21. Polymorphic form according to claim 20, characterised in that in produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 13.40, 12.28, 8.54, 7.32, 6.17, 5.11, 5.01, 4.65, 4.60, 4.48, 4.44, 4.27, 4.19, 4.10, 4.02, 3.97, 3.83, 3.66, 3.54, 3.42, 3.20, 2.91, 2.58 (Å).

22. Polymorphic form of the laevorotatory or the dextrorotatory enantiomer of modafinil described as Form IV, characterised in that it produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 12.38, 8.58, 7.34, 5.00, 4.09 (Å).

23. Polymorphic form according to claim 22, characterised in that in produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 13.88, 12.38, 10.27; 8.58, 7.34, 6.16, 5.660, 5.120, 5.00, 4.64, 4.48, 4.26, 4.18, 4.09, 3.82, 3.66, 3.53, 3.42 , 3.28, 3.20 (Å).

24. Polymorphic form of the laevorotatory or the dextrorotatory enantiomer of modafinil, characterised in that it produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings 9.63, 5.23, 5.03, 4.74, 4.66, 4.22, 4.10, 3.77 (Å).

25. Dimethyl carbonate solvate of the laevorotatory or the dextrorotatory enantiomer of modafinil, characterised in that it produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 12.31, 9.69, 9.09, 8.54, 7.27, 6.21, 5.45, 5.10, 5.00, 4.83, 4.63, 4.46, 4.22, 4.13, 4.09, 3.78, 3.62, 3.53, 3.42, 3.32, 3.24, 3.21, 3.10 (Å).

26. Process of conversion of a first crystalline form of one of the enantiomers of modafinil into a second crystalline form of the said enantiomer which is different from the first, the said process comprising the following stages :

i) suspending the said first crystalline form of the said modafinil enantiomer in an appropriate solvent, and

ii) recovering the said second crystalline form obtained.

27. Process according to claim 26, in which the enantiomer used is (-)-modafinil.

28. Process according to claim 27, in which the first crystalline form is form I.

29. Process according to claim 28, in which the solvent used in stage ii) is acetonitrile, as a result of which an acetonitrile solvate is obtained.

30. Acetonitrile solvate of the (-)-modafinil or (+)-modafinil enantiomer, characterised in that it produces an X-ray diffraction spectrum comprising intensity peaks at the interplanar spacings : 16.17, 14.14, 12.32, 10.66, 9.79, 9.29, 8.54, 8.15, 7.80, 7.09, 6.31, 5.83, 5.62, 5.41, 5.10, 4.90, 4.66, 4.58, 4.46, 4.33, 4.20, 4.02, 3.92, 3.835, 3.72, 3.60, 3.57; 3.45, 3.33, 3.24, 3.19, 3.09, 3.03.

31. Process for the preparation of optically active modafinil from modafinil acid, comprising the following stages :

i) separating the two optical enantiomers of (±)-modafinil acid and recovering at least one of the enantiomers,

ii) placing one of the two enantiomers obtained in contact with a lower alkyl haloformate in the presence of alcohol or an organic base,

iii) recovering the product obtained,

iv) converting the ester obtained into an amide,

v) recovering the product obtained in stage iv).

32. Process according to claim 31, in which the haloformate is a lower alkyl chloroformate.

33. Process according to claim 32, in which the lower alkyl chloroformate is methyl chloroformate.

34. Process according to any one of claims 31 to 33, in which the base used in stage ii) is selected from triethylamine, diisopropylamine, diethylmethylamine, DBU.

35. Process according to any one of claims 31 to 34, in which the solvent used in stage ii) is a lower aliphatic alcohol, preferably methanol.

36. Process according to any one of claims 31 to 35, in which the solvent used in stage iv) is a lower aliphatic alcohol, preferably methanol.

37. Process according to any one of claims 31 to 36, in which resolution of the optical enantiomers of (±)-modafinil acid in stage i) is carried out through a preferential crystallisation process.

38. Process according to claim 37, in which the process of resolving the two optical enantiomers of (±) modafinil acid or the salts of the same is a seeded process, the said process comprising the following stages :

a) homogenising at a temperature T_D a combination comprising the racemic mixture of crystals of the first enantiomer of modafinil acid and solvent in the form of conglomerate, for which the defining point E defined by the concentration and temperature variables T_D lies in the monophase domain of the dilute solution,

b) rapidly cooling the solution prepared in stage a) initially at the temperature T_D down to temperature T_F,

c) seeding the solution in stage b) during or at the end of cooling (T_F) with very pure seeds of the first enantiomer,

d) harvesting the crystals of the first enantiomer,

e) adding the racemic mixture of crystals in the form of conglomerate to the mother liquors resulting from the harvest performed in stage d) and homogenising the new combination by heating to a temperature T_D, in such a way that the defining point E' is symmetrical for E with respect to the plane of the racemic mixture of the solvent, (-)-antipode, (+)-antipode system, the said point E' being located in the monophase domain of the dilute solution,

f) rapidly cooling the solution obtained in stage e), initially at the temperature T_D, down to the temperature T_F,

g) seeding the solution obtained in stage f) using very pure seeds of the second enantiomer,

h) harvesting crystals of the second enantiomer,

i) adding the racemic mixture in the form of a conglomerate of crystals to the mother liquors resulting from the crystal harvests performed in stage h) and homogenising the new combination heating to a temperature T_D to obtain a composition which is identical to that of the combination having the initial defining point E,

j) repeating stages a), b), c), d), e), f), h) and j) in order to obtain the first and then the second of the two enantiomers in succession.

39. Process according to claim 37, in which the process of separation of the two optical enantiomers of (±)-modafinil acid or salts of the same by preferential crystallisation is a self-seeded AS3PC process, the said process comprising the following stages :

a) creating a combination comprising the racemic mixture of crystals of the first enantiomer of modafinil acid and solvent, in the form of conglomerate, for which the defining point E defined by the concentration and

temperature variables T_B is located in the two-phase domain of the enantiomer in excess and is in equilibrium with its saturated solution,

b) applying a function for programming cooling from the temperature of the two-phase mixture prepared in stage a), the said programming function being such that the mother liquors remain slightly supersaturated encouraging growth of the enantiomer present in the form of crystals while preventing spontaneous nucleation, of the second enantiomer present in the solution,

c) adopting a stirring speed which increases slightly over time throughout the period of crystal growth in stage b) in such a way that the stirring speed is at all times sufficiently slow to encourage growth of the first enantiomer while preventing the generation of excessively large shear forces giving rise to uncontrolled nucleation and sufficiently fast to produce a homogeneous suspension and rapid renewal of the mother liquor about each crystallite of the first enantiomer,

d) harvesting crystals of the first enantiomer,

e) adding the racemic mixture of crystals in the form of conglomerate to the mother liquors resulting from the harvest performed in stage d) and bringing the new combination to a temperature plateau T_B for the time necessary to achieve thermodynamic equilibrium so that the defining point E' is symmetrical for E with respect to the plane of the racemic mixtures of the solvent, (-)-antipode, (+)-antipode system, the said point E' being located within the two-phase domain of the second enantiomer in excess and in equilibrium with its saturated solution,

f) applying the same cooling programming function as in stage b) to the two-phase mixture prepared in stage e) containing the second enantiomer in such a way that the mother liquors remain slightly supersaturated during crystallisation so as to encourage growth of the enantiomer present in the form of crystals while preventing spontaneous nucleation of the first enantiomer present in the solution,

g) adopting a stirring speed which increases slightly over time throughout the period of crystalline growth in stage f) in such a way that at all times it is sufficiently slow to encourage growth of the second enantiomer while

avoiding generating excessively large shear forces bringing about uncontrolled nucleation, and sufficiently fast to achieve a homogeneous suspension and rapid renewal of the mother liquor around each crystallite of the second enantiomer,

h) harvesting crystals of the second enantiomer,

i) adding the racemic mixture of crystals in the form of conglomerate to the mother liquors resulting from the crystal harvest performed in stage g) in order to obtain a combination whose composition is identical to that of the initial combination E,

j) repeating stages a), b), c), d), e), f) g), h) and i) to obtain the first and then the second of the two enantiomers in succession.

40. Process according to claim 39, characterised in that in stage a) choice of the solvent or solvents and the working temperature range are defined in such a way as to have simultaneously:

- antipodes forming a conglomerate and of which any racemate is metastable within the working temperature range,
- liquors which are sufficiently concentrated but of low viscosity and low vapour pressure,
- the absence of solvolysis and racemisation,
- stability of the solvates if these are present at equilibrium and they are in the form of separable enantiomers.

41. Process according to any one of claims 39 to 40, characterised in that in stages (a) and (e) temperature T_B is higher than temperature T_L for homogenisation of the quantity of racemic mixture present in the initial suspension, and in that from the curve for the variation of T_{HOMO} in relation to the enantiomer excess and for a constant concentration of racemic mixture X_L the said temperature T_B is defined in such a way that the mass of fine crystals of the first enantiomer in stages (a) and (i) and the second enantiomer in stage (e) in equilibrium with their saturated solutions represents at most 50% and preferably between approximately 25% and 40% of the expected harvest.

42. Process according to any one of claims 39 to 41, characterised in that in stages (b) and (f) the programming function for cooling the temperature T_B to T_F appropriate for the experimental assemblage is defined in such a way as to:

- achieve slight supersaturation throughout the period for crystallisation of the enantiomer present in the form of crystals at the start of each cycle, this slight supersaturation bringing about gentle growth and secondary nucleation,
- achieve maximum supersaturation of the other enantiomer at T_F without primary nucleation,
- obtaining a harvest of crystals in stages (d) and (h) which after addition of the racemic mixture and making-up in stages (e) and (i), makes it possible for the operations to be cyclical.

43. Process according to claim 42, characterised in that the cooling programming function is determined for its part from T_L to T_F by cooling of the solution of concentration X_L from T_L + 1°C to T_F, T_F being below $T_L - (T_{HOMO} - T_L)$, in order to obtain a stable saturated solution without primary nucleation while allowing a double harvest of the initial enantiomer excess and in that the said cooling programming function is determined for its part from T_B to T_L by extrapolation of the same function as determined from T_L + 1°C to T_F.

44. Process according to any one of claims 39 to 43, characterised in that in the two stages (b) and (f) the heat release accompanying deposition of the first enantiomer and the second enantiomer is incorporated into the cooling programming function.

45. Process according to any of claims 39 to 44, characterised in that in stages (e) and (i) shortages of solvent are made up.

46. Process according to any one of claims 39 to 45, characterised in that in stages (a), (e) and (i) the fine crystals of racemic mixture in the form of conglomerate, which are added, were before being introduced subjected to prior

treatment accelerating the dissolution stage, such as grinding and sieving, treatment with ultrasound waves or partial lyophilisation.

47. Process according to any one of claims 39 to 46, characterised in that in stages (a), (e) and (i), the stirring speed is increased.

48. Process according to any one of claims 38 or 39 to 47, in which the solvent used in stage a) is ethanol, 2-methoxyethanol or methanol.

49. Process according to claim 48, in which the temperature T_F lies between 0 and 40°C.

50. Process according to either of claims 48 or 49, in which the concentration of the racemic mixture in stage a) lies between 2 and 50 % by mass.

51. Process according to any one of claims 48 to 50, in which the enantiomer excess in stage a) lies between 1 and 50 % by mass.

52. Process according to claim 51, in which the temperature T_B lies between 25°C and 50°C.

53. Process according to any one of claims 48 to 52, in which duration of the temperature plateau T_B lies between 15 and 60 min.

54. Process for preparation of one of the enantiomers of modafinil comprising the following stages :

a) separating the two optical enantiomers of (±)-modafinil acid or salts of the same through a preferential crystallisation process as defined in claims 35 to 53,
b) converting the said enantiomer to an amide,
c) recovering the modafinil enantiomer obtained.

55. Process according to claim 54, in which stage b) is carried out in two stages:

b1) conversion of the said enantiomer into a lower alkyl ester,

b2) converting the product obtained in stage b1) to an amide.

56. Pharmaceutical composition comprising the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form (II), in association if appropriate with a pharmaceutically acceptable vehicle.

57. Pharmaceutical composition comprising the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form (III), in association if appropriate with a pharmaceutically acceptable vehicle.

58. Pharmaceutical composition comprising the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form (IV), in association if appropriate with a pharmaceutically acceptable vehicle.

59. Pharmaceutical composition comprising the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form (V), in association if appropriate with a pharmaceutically acceptable vehicle.

60. Use of the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form II for the manufacture of a pharmaceutical intended for the prevention or treatment of a disease selected from hypersomnia, including in particular idiopathic hypersomnia and hypersomnia in patients affected by a cancer treated with morphine analgesics to relieve pain; sleep apnoeas, excessive somnolence associated with a disease, obstructive sleep apnoeas, narcolepsy, somnolence, excessive somnolence, excessive somnolence associated with narcolepsy; disturbances of the central nervous system such as Parkinson's disease; protection of the cerebral tissue against ischaemia, alertness disturbances, in particular alertness disturbances associated with Steinert's disease, attention disturbances, for example associated with hyperactivity (ADHD), the condition of

fatigue, in particular that associated with multiple sclerosis and other degenerative diseases; depression, the depressive condition associated with low exposure to sunlight, schizophrenia, rotating shift work, time shifts; eating disturbances in which modafinil acts as an appetite stimulant, the stimulation of cognitive functions in low doses.

61. Use of the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form III for the manufacture of a pharmaceutical intended for the prevention or treatment of a disease selected from hypersomnia, including in particular idiopathic hypersomnia and hypersomnia in patients affected by a cancer treated with morphine analgesics to relieve pain; sleep apnoeas, excessive somnolence associated with a disease, obstructive sleep apnoeas, narcolepsy, somnolence, excessive somnolence, excessive somnolence associated with narcolepsy; disturbances of the central nervous system such as Parkinson's disease; protection of the cerebral tissue against ischaemia, alertness disturbances, in particular alertness disturbances associated with Steinert's disease, attention disturbances, for example associated with hyperactivity (ADHD), the condition of fatigue, in particular that associated with multiple sclerosis and other degenerative diseases; depression, the depressive condition associated with low exposure to sunlight, schizophrenia, rotating shift work, time shifts; eating disturbances in which modafinil acts as an appetite stimulant, the stimulation of cognitive functions in low doses

62. Use of the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form IV for the manufacture of a pharmaceutical intended for the prevention or treatment of a disease selected from hypersomnia, including in particular idiopathic hypersomnia and hypersomnia in patients affected by a cancer treated with morphine analgesics to relieve pain; sleep apnoeas, excessive somnolence associated with a disease, obstructive sleep apnoeas, narcolepsy, somnolence, excessive somnolence, excessive somnolence associated with narcolepsy; disturbances of the central nervous system such as Parkinson's disease; protection of the cerebral tissue against ischaemia, alertness disturbances, in particular alertness disturbances associated with Steinert's disease, attention disturbances, for example associated with hyperactivity (ADHD), the condition of

fatigue, in particular that associated with multiple sclerosis and other degenerative diseases; depression, the depressive condition associated with low exposure to sunlight, schizophrenia, rotating shift work, time shifts; eating disturbances in which modafinil acts as an appetite stimulant, the stimulation of cognitive functions in low doses.

63. Use of the polymorphic form of (-)-modafinil or of (+)-modafinil, described as form V for the manufacture of a pharmaceutical intended for the prevention or treatment of a disease selected from hypersomnia, including in particular idiopathic hypersomnia and hypersomnia in patients affected by a cancer treated with morphine analgesics to relieve pain; sleep apnoeas, excessive somnolence associated with a disease, obstructive sleep apnoeas, narcolepsy, somnolence, excessive somnolence, excessive somnolence associated with narcolepsy; disturbances of the central nervous system such as Parkinson's disease; protection of the cerebral tissue against ischaemia, alertness disturbances, in particular alertness disturbances associated with Steinert's disease, attention disturbances, for example associated with hyperactivity (ADHD), the condition of fatigue, in particular that associated with multiple sclerosis and other degenerative diseases; depression, the depressive condition associated with low exposure to sunlight, schizophrenia, rotating shift work, time shifts; eating disturbances in which modafinil acts as an appetite stimulant, the stimulation of cognitive functions in low doses.